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APPROVAL PACKAGE FOR:

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APPROVED

ELLENCE™
epirubicin hydrochloride injection

SEP 15 1999

WARNING

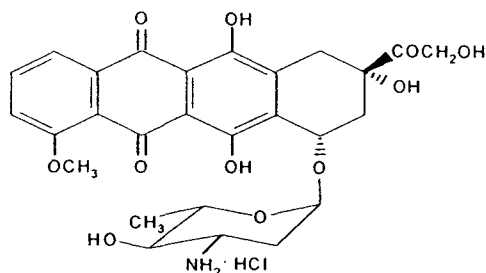
1. Severe local tissue necrosis will occur if there is extravasation during administration (See PRECAUTIONS). Epirubicin must not be given by the intramuscular or subcutaneous route.
2. Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with epirubicin or months to years after termination of therapy. The probability of developing clinically evident CHF is estimated as approximately 0.9% at a cumulative dose of 550 mg/m², 1.6% at 700 mg/m², and 3.3% at 900 mg/m². In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m². The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m²; this cumulative dose should only be exceeded with extreme caution. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with ELLENCE may occur at lower cumulative doses whether or not cardiac risk factors are present.
3. Secondary acute myelogenous leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines, including epirubicin. The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The cumulative risk of developing treatment-related AML, in 3846 patients with breast cancer who received adjuvant treatment with epirubicin-containing regimens, was estimated as 0.2% at 3 years and 0.8% at 5 years.
4. Dosage should be reduced in patients with impaired hepatic function (See DOSAGE AND ADMINISTRATION).
5. Severe myelosuppression may occur.
6. Epirubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

ELLENCE Injection (epirubicin hydrochloride injection) is an anthracycline cytotoxic agent intended for intravenous administration. ELLENCE is supplied as a sterile, clear, red solution and is available in polypropylene vials containing 50 and 200 mg of epirubicin hydrochloride as a preservative-free, ready-to-use solution. Each milliliter of solution contains 2 mg of epirubicin hydrochloride. Inactive ingredients include sodium chloride, USP, and water for injection, USP. The pH of the solution has been adjusted to 3.0 with hydrochloric acid, NF.

Epirubicin hydrochloride is the 4'-epimer of doxorubicin and is a semi-synthetic derivative of daunorubicin. The chemical name is (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride. The active ingredient is a red-orange hygroscopic powder,

1 with the empirical formula $C_{27}H_{29}NO_{11}HCl$ and a molecular weight of 579.95. The structural
2 formula is as follows:



CLINICAL PHARMACOLOGY

5
6
7
8
9
10 Epirubicin is an anthracycline cytotoxic agent. Although it is known that anthracyclines can
11 interfere with a number of biochemical and biological functions within eukaryotic cells, the
12 precise mechanisms of epirubicin's cytotoxic and/or antiproliferative properties have not been
13 completely elucidated.

14
15 Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide
16 base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis.
17 Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytotoxic activity.
18 Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-
19 stranded DNA and interfering with replication and transcription. Epirubicin is also involved in
20 oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and
21 cytotoxic activity of epirubicin is thought to result from these or other possible mechanisms.

22
23 Epirubicin is cytotoxic in vitro to a variety of established murine and human cell lines and
24 primary cultures of human tumors. It is also active in vivo against a variety of murine tumors
25 and human xenografts in athymic mice, including breast tumors.
26

Pharmacokinetics in Special Populations

Age. A population analysis of plasma data from 36 cancer patients (13 males and 23 females, 20 to 73 years) showed that age affects plasma clearance of epirubicin in female patients. The predicted plasma clearance for a female patient of 70 years of age was about 35% lower than that for a female patient of 25 years of age. An insufficient number of males > 50 years of age were included in the study to draw conclusions about age-related alterations in clearance in males. Although a lower epirubicin starting dose does not appear necessary in elderly female patients, and was not used in clinical trials, particular care should be taken in monitoring toxicity when epirubicin is administered to female patients > 70 years of age. (See PRECAUTIONS.)

Gender. In patients ≤ 50 years of age, mean clearance values in adult male and female patients were similar. The clearance of epirubicin is decreased in elderly women (see Pharmacokinetics in Special Populations – Age).

Pediatric. The pharmacokinetics of epirubicin in pediatric patients have not been evaluated.

Race. The influence of race on the pharmacokinetics of epirubicin has not been evaluated.

Hepatic Impairment. Epirubicin is eliminated by both hepatic metabolism and biliary excretion and clearance is reduced in patients with hepatic dysfunction. In a study of the effect of hepatic dysfunction, patients with solid tumors were classified into 3 groups. Patients in Group 1 (n=22) had serum AST (SGOT) levels above the upper limit of normal (median: 93 IU/L) and normal serum bilirubin levels (median: 0.5 mg/dL) and were given epirubicin doses of 12.5 to 90 mg/m². Patients in Group 2 had alterations in both serum AST (median: 175 IU/L) and bilirubin levels (median: 2.7 mg/dL) and were treated with an epirubicin dose of 25 mg/m² (n=8). Their pharmacokinetics were compared to those of patients with normal serum AST and bilirubin values, who received epirubicin doses of 12.5 to 120 mg/m². The median plasma clearance of epirubicin was decreased compared to patients with normal hepatic function by about 30% in patients in Group 1 and by 50% in patients in Group 2. Patients with more severe hepatic impairment have not been evaluated. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Renal Impairment. No significant alterations in the pharmacokinetics of epirubicin or its major metabolite, epirubicinol, have been observed in patients with serum creatinine < 5 mg/dL. A 50% reduction in plasma clearance was reported in four patients with serum creatinine ≥ 5 mg/dL (see WARNINGS and DOSAGE AND ADMINISTRATION). Patients on dialysis have not been studied.

Drug-Drug Interactions

Taxanes. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when given immediately following the taxane.

Cimetidine. Coadministration of cimetidine (400 mg twice daily for 7 days starting 5 days before chemotherapy) increased the mean AUC of epirubicin (100 mg/m²) by 50% and decreased its plasma clearance by 30% (see PRECAUTIONS).

Drugs metabolized by cytochrome P-450 enzymes. No systematic in vitro or in vivo evaluation has been performed to examine the potential for inhibition or induction by epirubicin of oxidative cytochrome P-450 isoenzymes.

CLINICAL STUDIES

Two randomized, open-label, multicenter studies evaluated the use of ELLENCE Injection 100 to 120 mg/m² in combination with cyclophosphamide and fluorouracil for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease (Stage II or III). Study MA-5 evaluated 120 mg/m² of epirubicin per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). This study randomized premenopausal and perimenopausal women with one or more positive lymph nodes to an epirubicin-containing CEF-120 regimen or to a CMF regimen. Study GFEA-05 evaluated the use of 100 mg/m² of epirubicin per course in combination with fluorouracil and cyclophosphamide (FEC-100). This study randomized pre- and postmenopausal women to the FEC-100 regimen or to a lower-dose FEC-50 regimen. In the GFEA-05 study, eligible patients were either required to have ≥ 4 nodes involved with tumor or, if only 1 to 3 nodes were positive, to have negative estrogen- and progesterone-receptors and a histologic tumor grade of 2 or 3. A total of 1281 women participated in these studies. Patients with T4 tumors were not eligible for either study. Table 2 shows the treatment regimens that the patients received.

Table 2. Treatment Regimens Used in Phase 3 Studies of Patients with Early Breast Cancer

	Treatment Groups	Agent	Regimen
MA-5 ¹ N=716	CEF-120 (total, 6 cycles) ² N=356	Cyclophosphamide ELLENCE Fluorouracil	75 mg/m ² PO, d 1-14, q 28 days 60 mg/m ² IV, d 1 & 8, q 28 days 500 mg/m ² IV, d 1 & 8, q 28 days
	CMF (total, 6 cycles) N=360	Cyclophosphamide Methotrexate Fluorouracil	100 mg/m ² PO, d 1-14, q 28 days 40 mg/m ² IV, d 1 & 8, q 28 days 600 mg/m ² IV, d 1 & 8, q 28 days
GFEA-05 ³ N=565	FEC-100 (total, 6 cycles) N=276	Fluorouracil ELLENCE Cyclophosphamide	500 mg/m ² IV, d 1, q 21 days 100 mg/m ² IV, d 1, q 21 days 500 mg/m ² IV, d 1, q 21 days
	FEC-50 (total, 6 cycles) N=289	Fluorouracil ELLENCE Cyclophosphamide	500 mg/m ² IV, d 1, q 21 days 50 mg/m ² IV, d 1, q 21 days 500 mg/m ² IV, d 1, 21 days
	Tamoxifen 30 mg daily x 3 years, postmenopausal women, any receptor status		

¹In women who underwent lumpectomy, breast irradiation was to be administered after completion of study chemotherapy.

²Patients also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or fluoroquinolone for the duration of their chemotherapy.

³All women were to receive breast irradiation after the completion of chemotherapy.

In the MA-5 trial, the median age of the study population was 45 years. Approximately 60% of patients had 1 to 3 involved nodes and approximately 40% had ≥ 4 nodes involved with tumor. In the GFEA-05 study, the median age was 51 years and approximately half of the patients were postmenopausal. About 17% of the study population had 1 to 3 positive nodes and 80% of

patients had ≥ 4 involved lymph nodes. Demographic and tumor characteristics were well-balanced between treatment arms in each study.

The efficacy endpoints of relapse-free survival (RFS) and overall survival (OS) were analyzed using Kaplan-Meier methods in the intent-to-treat (ITT) patient populations in each study. Results for endpoints are described in terms of the outcomes at 5-years. In Study MA-5, epirubicin-containing combination therapy (CEF-120) showed significantly longer 5-year RFS than CMF (62% versus 53%; stratified logrank $p=0.013$). The overall reduction in risk of relapse was 24%. The 5-year OS was also greater for the epirubicin-containing CEF-120 regimen than for the CMF regimen (77% versus 70%; stratified logrank $p=0.043$; non-stratified logrank $p=0.13$). The overall relative reduction in the risk of death was 29%.

In Study GFEA-05, patients treated with the higher-dose epirubicin regimen (FEC-100) had a significantly longer 5-year RFS (65% versus 52%, logrank $p=0.007$) and OS (76% versus 65%, logrank $p=0.007$) than patients given the lower dose regimen (FEC-50). The overall reduction in risk of relapse was 32%. The relative reduction in the risk of death was 31%.

Although the trials were not powered for subset analyses, improvement in RFS and OS were observed both in patients with 1-3 nodes positive and in those with ≥ 4 nodes positive for tumor involvement when comparing the CEF-120 or FEC-100 groups with the control groups. In addition, in the GFEA-05 study, similar improvements in RFS and OS were observed in both pre- and postmenopausal women treated with FEC-100 compared to FEC-50. Efficacy results for the two studies are shown in Table 3.

Table 3. Efficacy Results from Phase 3 Studies of Patients with Early Breast Cancer*

	MA-5 Study		GFEA-05 Study	
	CEF-120 N=356	CMF N=360	FEC-100 N=276	FEC-50 N=289
RFS at 5 yrs (%)	62	53	65	52
Log-rank Test	(stratified $p=0.013$)		(p=0.007)	
OS at 5 yrs	77	70	76	65
Log-rank Test	(stratified $p=0.043$) (unstratified $p=0.13$)		(p=0.007)	

*Based on Kaplan-Meier estimates

of infection, symptoms of CHF, or injection-site pain occurs following therapy with ELLENCE. Patients should be informed that they will almost certainly develop alopecia. Patients should be advised that their urine may appear red for 1 to 2 days after administration of ELLENCE and that they should not be alarmed. Patients should understand that there is a risk of irreversible myocardial damage associated with treatment with ELLENCE, as well as a risk of treatment-related leukemia. Because epirubicin may induce chromosomal damage in sperm, men undergoing treatment with ELLENCE should use effective contraceptive methods. Women treated with ELLENCE may develop irreversible amenorrhea, or premature menopause.

Laboratory Testing

See WARNINGS. Blood counts, including absolute neutrophil counts and liver function should be assessed before and during each cycle of therapy with epirubicin. Repeated evaluations of LVEF should be performed during therapy.

Drug Interactions

ELLENCE when used in combination with other cytotoxic drugs may show on-treatment additive toxicity, especially hematologic and gastrointestinal effects.

Concomitant use of ELLENCE with other cardioactive compounds that could cause heart failure (e.g., calcium channel blockers), requires close monitoring of cardiac function throughout treatment.

There are few data regarding the coadministration of radiation therapy and epirubicin. In adjuvant trials of epirubicin-containing CEF-120 or FEC-100 chemotherapies, breast irradiation was delayed until after chemotherapy was completed. This practice resulted in no apparent increase in local breast cancer recurrence relative to published accounts in the literature. A small number of patients received epirubicin-based chemotherapy concomitantly with radiation therapy but had chemotherapy interrupted in order to avoid potential overlapping toxicities. It is likely that use of epirubicin with radiotherapy may sensitize tissues to the cytotoxic actions of irradiation. Administration of ELLENCE after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation.

Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity.

Cimetidine increased the AUC of epirubicin by 50%. Cimetidine treatments should be stopped during treatment with ELLENCE (see CLINICAL PHARMACOLOGY).

Drug-Laboratory Tests Interactions

There are no known interactions between ELLENCE and laboratory tests.

Carcinogenesis, Mutagenesis & Impairment of Fertility

See WARNINGS

Pregnancy

Pregnancy Category D - see WARNINGS

1 Nursing Mothers

2 Epirubicin was excreted into the milk of rats treated with 0.50 mg/kg/day of epirubicin during
3 peri- and postnatal periods. It is not known whether epirubicin is excreted in human milk.
4 Because many drugs, including other anthracyclines, are excreted in human milk and because of
5 the potential for serious adverse reactions in nursing infants from epirubicin, mothers should
6 discontinue nursing prior to taking this drug.

7 Geriatric Use

8 Although a lower starting dose of ELLENCE was not used in trials in elderly female patients,
9 particular care should be taken in monitoring toxicity when ELLENCE is administered to female
10 patients ≥ 70 years of age. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Special
11 Populations).
12

13 Pediatric Use

14 The safety and effectiveness of epirubicin in pediatric patients have not been established in
15 adequate and well-controlled clinical trials. Pediatric patients may be at greater risk for
16 anthracycline-induced acute manifestations of cardiotoxicity and for chronic CHF.
17

18 ADVERSE REACTIONS**19 On-Study Events**

20 Integrated safety data are available from two studies (Studies MA-5 and GFEA-05, see
21 CLINICAL STUDIES) evaluating epirubicin-containing combination regimens in patients with
22 early breast cancer. Of the 1260 patients treated in these studies, 620 patients received the
23 higher-dose epirubicin regimen (FEC-100/CEF-120), 280 patients received the lower-dose
24 epirubicin regimen (FEC-50), and 360 patients received CMF. Serotonin-specific antiemetic
25 therapy and colony-stimulating factors were not used in these trials. Clinically relevant acute
26 adverse events are summarized in Table 4.
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Table 4. Clinically Relevant Acute Adverse Events in Patients with Early Breast Cancer

Event	% of Patients					
	FEC-100/CEF-120 (N = 620)		FEC-50 (N = 280)		CMF (N = 360)	
	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4
Hematologic						
Leukopenia	80.3	58.6	49.6	1.5	98.1	60.3
Neutropenia	80.3	67.2	53.9	10.5	95.8	78.1
Anemia	72.2	5.8	12.9	0	70.9	0.9
Thrombocytopenia	48.8	5.4	4.6	0	51.4	3.6
Endocrine						
Amenorrhea	71.8	0	69.3	0	67.7	0
Hot flashes	38.9	4.0	5.4	0	69.1	6.4
Body as a Whole						
Lethargy	45.8	1.9	1.1	0	72.7	0.3
Fever	5.2	0	1.4	0	4.5	0
Gastrointestinal						
Nausea/vomiting	92.4	25.0	83.2	22.1	85.0	6.4
Mucositis	58.5	8.9	9.3	0	52.9	1.9
Diarrhea	24.8	0.8	7.1	0	50.7	2.8
Anorexia	2.9	0	1.8	0	5.8	0.3
Infection						
Infection	21.5	1.6	15.0	0	25.9	0.6
Febrile neutropenia	NA	6.1	0	0	NA	1.1
Ocular						
Conjunctivitis/keratitis	14.8	0	1.1	0	38.4	0
Skin						
Alopecia	95.5	56.6	69.6	19.3	84.4	6.7
Local toxicity	19.5	0.3	2.5	0.4	8.1	0
Rash/itch	8.9	0.3	1.4	0	14.2	0
Skin changes	4.7	0	0.7	0	7.2	0

FEC & CEF= cyclophosphamide+epirubicin+fluorouracil; CMF= cyclophosphamide+methotrexate+fluorouracil

NA = not available

Grade 1 or 2 changes in transaminase levels were observed but were more frequently seen with CMF than with CEF.

Delayed Events

Table 5 describes the incidence of delayed adverse events in patients participating in the MA-5 and GFEA-05 trials.

Table 5. Long-Term Adverse Events in Patients with Early Breast Cancer

Event	Percent of patients		
	FEC-100/CEF-120 (n=620)	FEC-50 (n=280)	CMF (n=360)
Cardiac toxicity			
Asymptomatic drops in LVEF	1.8%	1.4%	0.8%
CHF	1.5%	0.4%	0.3%
Leukemia			
AML	0.8%	0	0.3%

Two cases of acute lymphoid leukemia (ALL) were also observed in patients receiving epirubicin. However, an association between anthracyclines such as epirubicin and ALL has not been clearly established.

Overview of Acute and Delayed Toxicities

Hematologic—See WARNINGS

Gastrointestinal. A dose-dependent mucositis (mainly oral stomatitis, less often esophagitis) may occur in patients treated with epirubicin. Clinical manifestations of mucositis may include a pain or burning sensation, erythema, erosions, ulcerations, bleeding, or infections. Mucositis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations; most patients recover from this adverse event by the third week of therapy. Hyperpigmentation of the oral mucosa may also occur.

Nausea, vomiting, and occasionally diarrhea and abdominal pain can also occur. Severe vomiting and diarrhea may produce dehydration. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before therapy (see PRECAUTIONS).

Cutaneous and Hypersensitivity Reactions. Alopecia occurs frequently, but is usually reversible, with hair regrowth occurring within 2 to 3 months from the termination of therapy. Flushes, skin and nail hyperpigmentation, photosensitivity, and hypersensitivity to irradiated skin (radiation-recall reaction) have been observed. Urticaria and anaphylaxis have been reported in patients treated with epirubicin; signs and symptoms of these reactions may vary from skin rash and pruritus to fever, chills, and shock.

Cardiovascular—See WARNINGS

Secondary Leukemia—See WARNINGS

Injection-Site Reactions—see PRECAUTIONS.

OVERDOSAGE

A 36-year-old man with non-Hodgkin's lymphoma received a daily 95 mg/m² dose of ELLENCE Injection for 5 consecutive days. Five days later, he developed bone marrow aplasia, grade 4 mucositis, and gastrointestinal bleeding. No signs of acute cardiac toxicity were observed. He was treated with antibiotics, colony-stimulating factors, and antifungal agents, and recovered completely. A 63-year-old woman with breast cancer and liver metastasis received a single 320 mg/m² dose of ELLENCE. She was hospitalized with hyperthermia and developed multiple organ failure (respiratory and renal), with lactic acidosis, increased lactate dehydrogenase, and anuria. Death occurred within 24 hours after administration of ELLENCE. Additional instances of administration of doses higher than recommended have been reported at doses ranging from 150 to 250 mg/m². The observed adverse events in these patients were qualitatively similar to known toxicities of epirubicin. Most of the patients recovered with appropriate supportive care.

If an overdose occurs, supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony-stimulating factors, and intensive care as needed) should be provided until the recovery of toxicities. Delayed CHF has been observed months after anthracycline administration. Patients must be observed carefully over time for signs of CHF and provided with appropriate supportive therapy.

DOSAGE AND ADMINISTRATION

ELLENCE Injection is administered to patients by intravenous infusion. ELLENCE is given in repeated 3- to 4-week cycles. The total dose of ELLENCE may be given on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle. The recommended dosages of ELLENCE are as follows:

Starting Doses

The recommended starting dose of ELLENCE is 100 to 120 mg/m². The following regimens were used in the trials supporting use of ELLENCE as a component of adjuvant therapy in patients with axillary-node positive breast cancer:

CEF-120:	Cyclophosphamide	75 mg/m ² PO D 1-14
	ELLENCE	60 mg/m ² IV D 1, 8
	5-Fluorouracil	500 mg/m ² IV D 1, 8
	Repeated every 28 days for 6 cycles	

FEC-100:	5-Fluorouracil	500 mg/m ²
	ELLENCE	100 mg/m ²
	Cyclophosphamide	500 mg/m ²
	All drugs administered intravenously on day 1 and repeated every 21 days for 6 cycles	

Patients administered the 120-mg/m² regimen of ELLENCE also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole (e.g., Septra®, Bactrim®) or a fluoroquinolone.

Bone Marrow Dysfunction. Consideration should be given to administration of lower starting doses (75-90 mg/m²) for heavily pretreated patients, patients with pre-existing bone marrow depression, or in the presence of neoplastic bone marrow infiltration (see WARNINGS and PRECAUTIONS).

Hepatic Dysfunction. Definitive recommendation regarding use of ELLENCE in patients with hepatic dysfunction are not available because patients with hepatic abnormalities were excluded from participation in adjuvant trials of FEC-100/CEF-120 therapy. In patients with elevated serum AST or serum total bilirubin concentrations, the following dose reductions were recommended in the clinical trials, although few patients experienced hepatic impairment:

- Bilirubin 1.2 to 3 mg/dL or AST 2 to 4 times upper limit of normal
1/2 of recommended starting dose
- Bilirubin > 3 mg/dL or AST > 4 times upper limit of normal
1/4 of recommended starting dose.

Information regarding experience in patients with hepatic dysfunction is provided in CLINICAL PHARMACOLOGY, Pharmacokinetics In Special Populations.

Renal Dysfunction. While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, lower doses should be considered in patients with severe renal impairment (serum creatinine >5 mg/dL).

Dose Modifications

Dosage adjustments after the first treatment cycle should be made based on hematologic and nonhematologic toxicities. Patients experiencing during treatment cycle nadir platelet counts $<50,000/\text{mm}^3$, absolute neutrophil counts (ANC) $<250/\text{mm}^3$, neutropenic fever, or Grades 3/4 nonhematologic toxicity should have the Day 1 dose in subsequent cycles reduced to 75% of the Day 1 dose given in the current cycle. Day 1 chemotherapy in subsequent courses of treatment should be delayed until platelet counts are $\geq 100,000/\text{mm}^3$, ANC $\geq 1,500/\text{mm}^3$, and nonhematologic toxicities have recovered to \leq Grade 1.

For patients receiving a divided dose of ELLENCE (Day 1 and Day 8), the Day 8 dose should be 75% of Day 1 if platelet counts are 75,000-100,000/ mm^3 and ANC is 1000 to 1499/ mm^3 . If Day 8 platelet counts are $<75,000/\text{mm}^3$, ANC $<1000/\text{mm}^3$, or Grade 3/4 nonhematologic toxicity has occurred, the Day 8 dose should be omitted.

Preparation & Administration Precautions

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Protective measures. The following protective measures should be taken when handling ELLENCE:

- Personnel should be trained in appropriate techniques for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling ELLENCE should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for syringe preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning (including gloves) should be placed in high-risk, waste-disposal bags for high temperature incineration.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All contaminated and cleaning materials should be placed in high-risk, waste-disposal bags for incineration. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

Incompatibilities. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. ELLENCE should not be mixed with heparin or fluorouracil due to chemical incompatibility that may lead to precipitation.

ELLENCE can be used in combination with other antitumor agents, but it is not recommended that it be mixed with other drugs in the same syringe.

Preparation of Infusion Solution

ELLENCE is provided as a preservative-free, ready-to-use solution.

Intravenous administration of ELLENCE should be performed with caution. It is recommended that ELLENCE be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution) over a period of 3 to 5 minutes. This technique is

intended to minimize the risk of thrombosis or perivenous extravasation, which could lead to severe cellulitis, vesicitation, or tissue necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein (see PRECAUTIONS). ELLENCE should be used within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

HOW SUPPLIED

ELLENCE Injection is available in polypropylene single-use vials containing 2 mg epirubicin hydrochloride per mL as a sterile, preservative-free, ready-to-use solution in the following strengths:

50 mg/25 mL single-use vial	NDC XXXX-XXXX-XX
200 mg/100 mL single-use vial	NDC XXXX-XXXX-XX

Store refrigerated between 2°C and 8°C (36°F and 46°F). Do not freeze. Protect from light.

Discard unused portion.

Rx only

Manufactured for: Pharmacia & Upjohn Company, Kalamazoo, MI 49001 USA

By: Pharmacia & Upjohn (Perth) Pty Limited, Bentley WA 6102 Australia

[915pi_C]

Sept 15, 1999

<p>Rx only See package insert for complete product information. Contains no preservative. Discard unused portion. Store refrigerated, 2°-8°C (36°-46°F). Do not freeze. Protect from light. 817 914 0000 Pharmacia & Upjohn Company</p>	<p>NDC 0009-5091-01</p> <p>ELLENCETM epirubicin hydrochloride Injection</p> <p>50 mg/25 mL (2 mg/mL)</p> <p>Single Use 25 mL Vial For Intravenous Use Only</p>
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Pharmacia & Upjohn
 Composition Unit 2566

Black

PMS
301

PMS
158

PRODUCT ELLENCETM		CCS # 4688-04
EDP # 692551	COPY CODE # 817 914 0000	COMPOSITION ORDER # 7302
SIZE 2.992 x 1.2"	IMPRINT SIZE 8MM	DRAWING # PD2272
DATE 8/26/99	TYPESET BY LA	ADDITIONAL INFORMATION No Varnish On Imprint Area

Size: 76 x 30.5MM



BLANK AREA
FOR IMPRINT
41.5X15MM
NO VARNISH

50 mg/25 mL
epirubicin
hydrochloride Injection
ELLENCETM
NDC 0009-5091-01

Rx only

See package insert for complete product information.
Contains no preservative.
Discard unused portion.

Store refrigerated,
2°-8°C (36°-46°F).
Do not freeze.
Protect from light.

Each mL contains:
epirubicin
hydrochloride 2 mg
sodium chloride, USP 9 mg
water for
Injection, USP qs
The pH of the solution has
been adjusted to 3.0 with
hydrochloric acid.

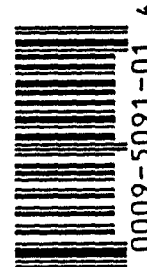
Caution: Cytotoxic Agent

NDC 0009-5091-01

ELLENCETM
epirubicin
hydrochloride
Injection

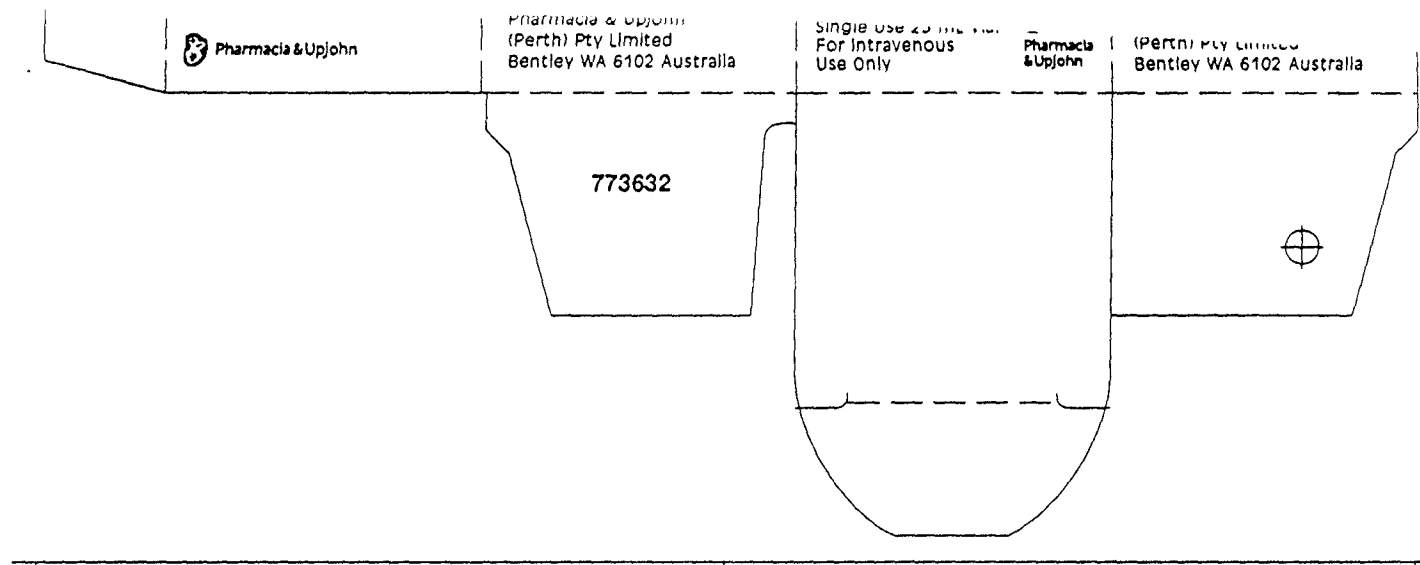
50 mg/25 mL
(2 mg/mL)

Manufactured for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA



0009-5091-01 4

Manufactured for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA



Pharmacia & Upjohn
Composition Unit 2566

Black

PMS
301

PMS
158

PRODUCT ELLECE		CCS # 4688-04	EDP # 773632	COPY CODE # 817 913 000D	COMPOSITION ORDER # 7303
SIZE 41.5x41.5x69.5 mm	IMPRINT SIZE 41.5x15 mm	DRAWING # PD2267	BOTTLE # N/A	DATE 8/26/99	TYPESET BY L. Amos
ADDITIONAL INFORMATION Imprint Area: Top Flap / No Varnish					

<p>R_x only See package insert for complete product information. Contains no preservative. Discard unused portion. Store refrigerated, 2°-8°C (36°-46°F). Do not freeze. Protect from light. 817 910 0000 Pharmacia & Upjohn Company</p>	<p>NDC 0009-5093-01</p>
	<p>ELLENCETM epirubicin hydrochloride Injection 200 mg/100 mL (2 mg/mL) Single Use 100 mL Vial For Intravenous Use Only</p>

Pharmacia&Upjohn

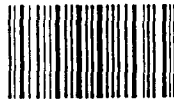
Composition Unit 2566

Black

PMS
301

PRODUCT ELLENCETM		CCS # 4688-06
EDP # 692551	COPY CODE # 817 910 0000	COMPOSITION ORDER # 7304
SIZE 2.992 x 1.2"	IMPRINT SIZE BMM	DRAWING # PD2272
DATE 8/26/99	TYPESET BY LA	ADDITIONAL INFORMATION No Varnish On Imprint Area

Size: 76 x 30.5MM



BLANK AREA
FOR IMPRINT
55X19MM
NO VARNISH

ELLENCETM
epirubicin
hydrochloride injection
200 mg/100 mL
(2 mg/mL)
NDC 0009-5093-01



Rx only
See package insert for complete
product information.

Contains no preservative.

Discard unused portion.

Store refrigerated, 2°-8°C (36°-46°F).
Do not freeze. Protect from light.

Each mL contains:
epirubicin hydrochloride 2 mg
sodium chloride, USP 9 mg
water for injection, USP qs

The pH of the solution has been adjusted
to 3.0 with hydrochloric acid.



Caution: Cytotoxic Agent

NDC 0009-5093-01

ELLENCETM
epirubicin
hydrochloride
injection

200 mg/100 mL
(2 mg/mL)



N
3 0009-5093-01 8



Manufactured for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
by:
Pharmacia & Upjohn (Perth) Pty Limited
Bentley WA 6102 Australia

Single Use 100 mL Vial
For Intravenous Use Only



Pharmacia
& Upjohn

Manufactured for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
by:
Pharmacia & Upjohn (Perth) Pty Limited
Bentley WA 6102 Australia

773476



Pharmacia & Upjohn

Composition Unit 2566

Black

PMS
301

PRODUCT ELLECE		CCS # 4688-06	EDP # 773476	COPY CODE # 817 909 000E	COMPOSITION ORDER # 7305
SIZE 55x53x101 mm	IMPRINT SIZE 55x19 mm	DRAWING # PD1991	BOTTLE # N/A	DATE 8/26/99	TYPESET BY L. Amos
ADDITIONAL INFORMATION Imprint Area: Top Flap / No Varnish					